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Cilia and Obesity

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Abstract

The ciliopathies Bardet – Biedl syndrome and Alström syndrome cause obesity. How ciliary dysfunction leads to obesity has remained mysterious, partly because of a lack of understanding of the physiological roles of primary cilia in the organs and pathways involved in the regulation of metabolism and energy homeostasis. Historically, the study of rare monogenetic disorders that present with obesity has informed our molecular understanding of the mechanisms involved in nonsyndromic forms of obesity. Here, we present a framework, based on genetic studies in mice and humans, of the molecular and cellular pathways underlying long-term regulation of energy homeostasis. We focus on recent progress linking these pathways to the function of the primary cilia with a particular emphasis on the roles of neuronal primary cilia in the regulation of satiety.

Introduction

The primary cilium has emerged as a clinically important organelle with ciliary dysfunction underlying several human syndromes collectively called the ciliopathies. Ciliopathies are associated with diverse phenotypes affecting nearly every tissue and organ system (see Braun and Hildebrandt 2016). Ciliopathies such as Bardet – Biedl syndrome (BBS) and Alström syndrome (ALMS) present with pediatric obesity as a clinical feature. Although an understanding of how ciliary defects cause certain ciliopathy-associated phenotypes, such as limb and neural tube defects, is emerging (see Bangs and Anderson 2016), how disrupted ciliary function leads to obesity remains poorly understood.

Here, we describe some neuroendocrine signaling pathways involved in the control of energy homeostasis in mammals, defects in which cause obesity in humans. We then describe how the use of mouse genetic models of ciliopathies has yielded interesting and sometimes contradictory results about the mechanisms through which primary cilia regulate body weight. In particular, we examine a potential role for cilia in the leptin–melanocortin signaling axis. We also discuss the *FTO* locus and a neighboring gene involved in ciliary

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function, *RPGRIP1L*, as influencing obesity through effects on leptin signaling. We close with a discussion on the emerging literature on the potential of adipocyte or preadipocyte cilia to impact metabolism and obesity. It is clear that the primary cilium, a long-neglected organelle, plays important roles in controlling mammalian energy homeostasis. Future studies on the roles of cilia in energy homeostasis may reveal therapeutic targets for this common disease.

I) Human Obesity and Ciliopathies

Pathophysiology of obesity—Obesity is an increase in energy stored as fat in sufficient magnitude to result in adverse health consequences, such as diabetes and cardiovascular disease. Mechanistically, obesity is caused by long-term caloric intake in excess of energy expenditure. The control of food intake and energy expenditure is accomplished through afferent signals that sense the energy status of the individual, integration in the brain including the hypothalamus, and efferent signals including those determining the intensity of hunger. One common misconception is that this physiological system is dedicated to the prevention of obesity. Instead, this system's essential role is the prevention of starvation and ensuring adequate energy intake to meet the energy requirements of basal metabolism, physical activity, growth, and reproduction.

Genetic predisposition to human obesity—Environmental influences, such as diet and exercise, interact with genetic factors to influence the onset and progression of weight gain. Genetic studies, including twin studies, have revealed that genetic variation accounts for 40% – 70% of weight variation, and that the heritability of obesity increases with its severity (Allison et al. 1996; O'Rahilly and Farooqi 2000). Both common genetic variants with small effects and rare genetic variants of larger effect contribute to the predisposition to obesity. The common genetic variants identified by genome-wide association studies (GWAS) have small, clinically insignificant effects individually. Most of these variants are located outside gene-coding regions, making it difficult to identify how they act. A case in point is the variant most strongly associated with obesity in multiple populations, a polymorphism present within an intron of the *FTO* gene (Frayling et al. 2007). One *FTO*-associated variant predisposes to obesity with an odds ratio of 1.3 to 1.7, which translates into a 2 – 3 kg weight gain. Even after extensive research efforts, the mechanism behind *FTO*-associated increases in weight remains unclear. We discuss below how the *FTO*-associated SNP may impact a neighboring gene, *RPGRIP1L*, encoding a critical component of the ciliary transition zone.

On the other end of the genetic effect spectrum from GWAS-identified single-nucleotide polymorphisms (SNPs), are single-gene defects that cause severe obesity, both in humans and mice. Analysis of these single genes has provided valuable insights into how energy stores are regulated in response to variable access to nutrition and demands for energy expenditure. Examples of single genes in which mutations cause human obesity include *LEPTIN* (*LEP*), its receptor (*LEPR*), *PROOPIOMELANOCORTIN* (*POMC*), *MELANOCORTIN RECEPTOR 4* (*MC4R*), and *SIM1*, all of which are components of the leptin–melanocortin system.

The Leptin-Melanocortin pathway regulates energy homeostasis—One major afferent signal allowing the brain to sense the level of energy stores is the hormone leptin (Zhang et al. 1994). This cytokine-like 167-amino-acid protein is released by adipocytes in proportion to fat mass. Decreasing leptin levels inform the brain of diminishing fat storage resulting from a negative energy balance, and compensatory effects on appetite and energy expenditure that can replenish the stores and reestablish energy balance. Leptin's action is mediated by the leptin receptor (LEPR), a single-transmembrane domain member of the class I cytokine receptor family. On binding to leptin, LEPR homodimerizes, leading to phosphorylation of JAK and STAT3. On phosphorylation, STAT3 dimerizes, translocates to the nucleus, and activates transcription of LEPTIN target genes (for a review on leptin signaling, see Myers et al. 2010).

The LEPTIN-responsive isoform of LEPR is expressed mainly in the hypothalamus, a brain region that interprets and integrates the peripheral signals that communicate energy balance. Within the hypothalamus, LEPTIN differentially affects the activity of two adjacent groups of neurons in the arcuate nucleus (ARC). LEPTIN inhibits the orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY) – producing neurons, and activates the anorexigenic proopiomelanocortin (POMC)-producing neurons. In these latter neurons, POMC is cleaved by the proteases proconvertase-1 and proconvertase-2 to generate the anorexigenic neuropeptide α -melanocyte-stimulating hormone (α -MSH)

Interactions between these neuronal populations within the ARC allow for cross talk and modulation of the neuronal output. The development of sophisticated inducible conditional alleles and reporters in mouse models has begun to reveal the complex regulation of subpopulations of neurons within the ARC (for recent reviews on ARC-mediated control of food intake, see Begg and Woods 2013; Mountjoy 2015)

AgRP/NPY and POMC-producing neurons in the ARC appear to respond directly to circulating signaling factors such as LEPTIN. These ARC neurons send axonal projections to second-order neurons in other regions of the hypothalamus, such as the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA), as well as to the hindbrain. Both α -MSH and AgRP act on a common G-proteincoupled receptor, melanocortin 4 receptor (MC4R), expressed by a subset of PVN neurons. α -MSH binds to and activates MC4R, whereas AgRP inhibits MC4R activity. To date, mutations in *MC4R* are the most common monogenic cause of severe human obesity, accounting for ~2.5% of cases. Similar to the POMC and AgRP neurons of the ARC, new tools have begun to reveal diversity among MC4R-expressing neurons and signaling mechanisms (Garfield et al. 2015; Ghamari-Langroudi et al. 2015). MC4R signaling and downstream neuronal circuitry remains an attractive target for therapeutics to treat obesity.

Human patients and mouse models mutant for components of the leptin–melanocortin pathway have helped reveal the physiological functions of this signaling system. For example, rare humans with complete LEPTIN deficiency show behaviors and physiological signs of starvation despite being extremely obese. LEPTIN replacement abolishes the hyperphagia, leading to normalization of weight, showing the necessary role for LEPTIN in regulating human energy homeostasis (Farooqi et al. 1999).

Although LEPTIN was initially thought to be a potential treatment for common obesity, all obese humans and animal models develop a resistance to LEPTIN's anorectic actions, despite having elevated adipose and thus increased circulating serum leptin levels. The molecular mechanisms associated with LEPTIN resistance are an active area of research and include altered transport of leptin across the blood–brain barrier, hypothalamic inflammation and ER stress, and diminished hypothalamic LEPTIN signaling (for a recent review of leptin resistance, see Aragonés et al. 2016).

Ciliopathies associated with obesity—Ciliopathies for which obesity is an integral component of the clinical presentation include BBS (OMIM #209900) and ALMS (OMIM #203800). In addition to obesity, BBS is characterized by retinal degeneration, postaxial polydactyly, and kidney cysts. Other associated findings include anosmia, mental retardation, hepatic fibrosis, and type 2 diabetes mellitus (Forsythe and Beales 2013). Obesity in patients with BBS ranges from mild to severe, and is reversible with caloric restriction and exercise (Beales et al. 1999). BBS is rare and genetically heterogeneous. To date, mutations in 21 genes, BBS1 – 21, have been identified that contribute to the development of the phenotype (see Braun and Hildebrandt 2016). Many BBS gene products form a large protein complex termed the BBSome (Nachury et al. 2007). The BBSome functions in the localization of select transmembrane proteins to, and removal from, the cilium (Berbari et al. 2008; Jin et al. 2010; Domire et al. 2011; Koemeter-Cox et al. 2014; Liew et al. 2014; Mourao et al. 2014).

Unlike the genetic heterogeneity underlying BBS, ALMS is associated with mutations in a single gene, *ALMS1*. Together with retinal degeneration and hearing loss, early-onset obesity is also one of the hallmarks. In addition, ALMS is associated with cardiomyopathy, liver and kidney dysfunction, and delayed puberty (for a review on ALMS, see Girard and Petrovsky 2011). Like BBS, the pathogenesis of ALMS has been linked to dysfunction of the primary cilium. The ALMS1 protein localizes to the centrosome and ciliary basal body and likely has a role in the formation or maintenance of primary cilia (Hearn et al. 2002; Li et al. 2007; Knorz et al. 2010). The human mutations that cause ALMS truncate ALMS1. These truncated proteins are able to support ciliogenesis, but may alter ciliary function or long-term maintenance, leading to the development of ALMS.

II) Lessons from Mouse Models of Cilia-associated Obesity

Mouse models of monogenic forms of obesity, which recapitulate the human phenotypes, have been invaluable for elucidating molecular mechanisms underlying the pathogenesis of obesity. Similarly, a better understanding of the role of the primary cilia in obesity and the relationship between cilia function and the leptin–melanocortin pathway has been driven by the study of mice carrying mutations affecting *Alms1* or BBS-associated genes, as well as by mice carrying conditional mutations affecting the formation and maintenance of primary cilia.

BBS and ALMS ciliopathy mouse models are obese—As in humans, mice mutant for many of the BBS-associated genes show obesity (Table 1) (Myktyyn et al. 2004; Nishimura et al. 2004; Davis et al. 2007). Mouse mutations that model ALMS include a

gene-trap (*Alms1*^{Gt(XH152)Byg}) and a spontaneous mutation (*fat aussie, foz*) (Collin et al. 2005; Arsov et al. 2006). Unlike *Bbs* mutant mice, *Alms1* mutant mice are born at a normal weight, similar to the clinical observations of ALMS in humans. Hyperphagia and obesity accompanied by hyperinsulinemia and type 2 diabetes occur postnatally in *Alms1* mutant mice.

Although *Bbs* and *Alms1* gene mutations cause obesity and *Bbs* and *Alms1* proteins are implicated in the function of the primary cilia, these observations do not show that the associated obesity is caused by alteration in cilia function, or that cilia are essential for the regulation of energy homeostasis.

Conditional disruption of primary cilia causes obesity in mice—Intraflagellar transport (IFT) is the process of protein transport within cilia critical for both their formation and maintenance. Conditional deletion of genes essential for IFT, such as *Ift88* or *Kif3a*, is useful for delineating when and where cilia are required for a specific phenotype. Inducing organism-wide loss of cilia in adult mice causes hyperphagia and subsequent obesity (Davenport et al. 2007). Restricting mice lacking cilia to the diet of control animals prevented obesity, indicating that cilia restrict weight gain by inhibiting the consumption of food rather than by affecting metabolism or locomotor activity. To test where cilia function to restrict food consumption, *Ift88* or *Kif3a* were removed exclusively in neurons using synapsin1-Cre (Davenport et al. 2007). As with organism-wide loss of cilia, removing cilia specifically in neurons causes obesity, strongly implicating neuronal cilia in the regulation of appetite and satiety.

The neurons involved in obesity-associated ciliopathy—As discussed above, the hypothalamus regulates appetite through neurons that make POMC or AgRP. Importantly, hypothalamic neurons each possess a single primary cilium, although the precise functions of these cilia are largely unknown. To address the role of cilia in these hypothalamic neurons, *Ift88* or *Kif3a* were conditionally removed in POMC or AgRP expressing neurons (Xu et al. 2005). By 6 weeks of age, mice lacking cilia on POMC-expressing neurons weighed significantly more than control mice, and continued to become obese during adulthood (Davenport et al. 2007). Mice lacking cilia on AgRP-expressing neurons did not show increased weight (NF Berbari and BK Yoder, unpubl.). In addition to obesity, mice lacking cilia on POMC-expressing neurons displayed increased levels of leptin, fasting serum glucose, and insulin. These increases were only present in obese mutants, not those kept at the control weight by pair feeding, indicating that these changes were secondary to obesity.

Potential Lepr involvement in ciliopathy-associated obesity—Although this work indicates that hypothalamic cilia restrain feeding, it does not reveal how they do so (Davenport et al. 2007). A suggestion of a molecular mechanism, *Bbs1*, a component of the BBSome, directly binds to *Lepr* and may participate in *Lepr* trafficking (Seo et al. 2009). Like mice lacking cilia on POMC-expressing neurons, *ad libitum* – fed *Bbs2*, *Bbs4*, and *Bbs6* mutant mice show elevated leptin levels (Rahmouni et al. 2008; Seo et al. 2009). Importantly, these *Bbs* mutants fail to reduce food intake in response to injection of leptin,

raising the possibility that a diminished response to leptin contributes to obesity in BBS (Rahmouni et al. 2008).

Nearly all obese mice and humans show elevated levels of circulating leptin, but this leptin is insufficient to suppress appetite, a phenomenon known as leptin resistance (Maffei et al. 1995; Considine et al. 1996). Thus, leptin resistance can either be a cause or a consequence of obesity. Interestingly, when caloric restriction was used to normalize leptin levels in *Bbs* mutant mice they still failed to respond to leptin with diminished food intake (Seo et al. 2009). The investigators concluded that leptin resistance was the primary deficit initiating hyperphagia and obesity in *Bbs* mice, but did not take into account the food anticipatory behavior that is observed on calorie restriction in mice. A growing literature reports that maintaining calorie restriction in rodents can have prolonged effects on meal structure and circadian rhythm (for a review on anticipatory feeding behavior, see Mistlberger 2009).

If both body composition and anticipatory feeding behavior are controlled for, adult mice lacking *Ift88*, or *Bbs* mutant mice, before the onset of obesity, display unaltered responses to leptin injected intraperitoneally (Berbari et al. 2013). *Lepr* activity was similar between these ciliopathy models and control mice, and other phenotypes associated with leptin and *LEPR* mutations, such as changes in thermoregulation and locomotor activity, are not present. These data suggest that cilia are not directly involved in leptin signaling (Berbari et al. 2013).

Very recent work by Guo et al. (2016) report a cilium-independent function of the BBSome. It appears to be required for trafficking of *Lepr* to the plasma membrane, and in *Bbs* mutants the obesity appears to be primarily a result of deficits in leptin sensitivity. This is in contrast to their findings with conditional loss of *IFT88* in which they report leptin resistance on increases in adiposity. This work begins to show that cilia mutant mouse models may display obesity through different and independent mechanisms (Fig. 1). This raises the exciting potential for cilia-mediated signaling and obesity to be broadly relevant beyond the rare ciliopathies.

Leptin-independent mechanisms by which neuronal cilia may affect energy homeostasis—Mutations affecting the mouse orthologs of BBS-associated genes, including *Bbs2*, *Bbs3*, and *Bbs4*, disrupt the localization of at least some GPCRs to their cilia, including melanin-concentrating hormone receptor 1 (*Mchr1*) (Berbari et al. 2008; Zhang et al. 2011).

Defective *Mchr1* signaling is an attractive candidate for mediating obesity in *Bbs* mutants, as *Mchr1* regulates feeding behavior. Either pharmacological or genetic activation of the *Mchr1* pathway is associated with hyperphagia, whereas repression is associated with anorectic behavior (Qu et al. 1996; Shimada et al. 1998; Ludwig et al. 2001; Borowsky et al. 2002; Chen et al. 2002). Thus, for *Mchr1* signaling to underlie obesity in *Bbs* mutants, the failure of *Mchr1* to reach the cilium would have to be associated with ectopic activation of *Mchr1* signaling. This is possible, although inactivation through sequestration in the cilium has not been previously described for GPCRs.

Apart from Mchr1, there is a growing list of other GPCRs that can preferentially localize to neuronal cilia. Some of these ciliary GPCRs include somatostatin receptor 3 (Sstr3), serotonin receptor 6 (5HT6), dopamine receptor 1 (Drd1), neuropeptide Y receptor 2 (Npy2r), and kisspeptin receptor 1 (Kiss1r) (Hamon et al. 1999; Handel et al. 1999; Brailov et al. 2000; Schulz et al. 2000; Marley and von Zastrow 2010; Domire et al. 2011; Loktev and Jackson 2013; Koemeter-Cox et al. 2014). While the functional significance of the localization of these receptors to cilia remains unclear, it is possible that they affect appetite, satiety, or metabolism, especially when given that somatostatin, serotonin, dopamine, neuropeptide Y, and kisspeptin, have all been implicated in either reward, feeding behaviors, metabolism, or glucose handling (Vijayan and McCann 1977; Pollock and Rowland 1981; Aponte et al. 1984; Salamone et al. 1990; Tolson et al. 2014).

Interestingly, *Alms^{foz/foz}* mice display a progressive loss of ciliary adenylyl cyclase III (Adcy3) in their hypothalamus, but no changes in Sstr3 or Mchr1 localization to cilia (Bishop et al. 2007; Heydet et al. 2013). Loss of Adcy3 function can itself cause obesity in mice through alterations in activity, hyperphagia, and leptin resistance (Wang et al. 2009). Conversely, a gain-of-function mutation in *Adcy3* confers protection from diet-induced obesity (Pitman et al. 2014). Future studies aimed at dissecting the roles of cilia GPCRs and their associated signaling proteins will shed light on cilia-associated changes in feeding behaviors, and other behaviors that neuronal cilia may modulate.

III) Relationship of the Transition Zone Protein Rpgrip11 to Obesity

Several common single nucleotide polymorphisms (SNPs) associated with obesity occur within the first intron of the *Fat Mass and Obesity-Associated (FTO)* gene (Dina et al. 2007; Frayling et al. 2007; Scuteri et al. 2007; Meyre et al. 2010). While studies have suggested mechanisms by which *Fto* can affect body weight, SNPs can alter regulatory elements that control the expression of distant genes, raising the possibility that *FTO*-associated SNPs may alter the expression of other genes. Chromatin conformation capture (3C) and circular chromosome conformation capture followed by high-throughput sequencing (4C-seq) revealed that, in addition to the *Fto* promoter, the region of the obesity-associated SNPs also interacts with the promoter of *Irx3*, a distant gene encoding a homeobox transcription factor (Smemo et al. 2014). At least in the human cerebellum, the presence of weight-associated SNPs and *Irx3* expression, but not *Fto* expression, were correlated (Smemo et al. 2014). Thus, SNPs within the *FTO* gene may affect the brain expression of *IRX3* to affect human body weight.

In addition to *IRX3*, *FTO* is nearby to *retinitis pigmentosa GTPase regulator-interacting protein-1 like (RPGRIP1L)*. *RPGRIP1L* encodes a key transition zone component involved in the localization of many other transition zone proteins (Liu et al. 2011; Williams et al. 2011). Like *Fto*, fasting lowers expression of *Rpgrip11* in the mouse hypothalamus (Stratigopoulos et al. 2011), suggesting that transcriptional regulation of *Rpgrip11* may control energy homeostasis. Homozygous mutations of mouse *Rpgrip11* cause embryonic phenotypes consistent with a severe disruption in ciliogenesis, complicating the analysis of how *Rpgrip11* may impact energy metabolism (Delous et al. 2007). However, heterozygous mice express half the normal levels of *Rpgrip11* protein (and wild-type levels of *Fto* and

Irx3), and are hyperphagic and fatter than wild-type controls (Stratigopoulos et al. 2014). The number of *Adcy3*-positive cilia in the ARC of *Rpgrip11*/heterozygotes is modestly reduced, suggesting that reduced expression of *Rpgrip11* may alter neuronal cilia, increasing feeding (Stratigopoulos et al. 2014). One of the *FTO* associated SNPs overlaps with a binding site for the p110 isoform of CUX1, a long-range transcriptional regulator that can affect *RPGRIP1L* expression in vitro (Stratigopoulos et al. 2011. Vagnais et al. 2013). Thus, diminished expression of this key transition zone component may alter ciliogenesis to account for how the *FTO* associated SNPs affect human weight. Future studies looking at conditional changes in *Rpgrip11* expression in development and the adult animal will help to elucidate the potential role for *Rpgrip11* in energy homeostasis.

IV) Potential Roles for Peripheral Cilia in Metabolic Regulation and Obesity

Functions for cilia in the central control of energy metabolism do not preclude additional roles for cilia relevant to obesity in peripheral tissues, including adipocytes. Like many mesenchymal cell types, preadipocytes can be ciliated (Marion et al. 2009; Zhu et al. 2009; Dalbay et al. 2015). Interestingly, preadipocytes are transiently ciliated during the transition from proliferation to terminal differentiation, leading to mature adipocytes that lack cilia (Marion et al. 2009). Interfering with ciliary function by knocking down BBS10 or BBS12 in human preadipocytes increased PPAR γ nuclear localization, a marker of adipogenesis (Marion et al. 2009). In contrast, knocking down *Ift88* in preadipocytes decreased PPAR γ levels and nuclear localization, and inhibited fat droplet formation, a marker of mature adipocytes (Zhu et al. 2009; Dalbay et al. 2015). Although it is not clear how these different manipulations of BBS-associated and ciliogenic genes relate to each other, one possibility is that cilia promote adipogenesis in a way that is restrained by the activity of BBS proteins.

One candidate for mediating the effects of cilia on adipogenesis is Hedgehog (Hh) signaling (see Bangs and Anderson 2016). Sustained activation of Hh signaling can suppress adipogenesis, and down-regulation of Hh signaling is concomitant with terminal differentiation of adipocytes (Cousin et al. 2006; Suh et al. 2006; Fontaine et al. 2008; James et al. 2010). The Hh pathway mediator Smoothened (Smo) localizes to preadipocyte cilia, suggesting that active ciliary Hh signaling may restrain premature differentiation into mature adipocytes (Marion et al. 2009), although there are differing data on whether Smo inhibition is sufficient to promote adipocyte differentiation (Suh et al. 2006; Fontaine et al. 2008; James et al. 2010). In most cell types, BBS proteins have minor roles in Hh signaling, but it will be interesting to determine whether down-regulation of Hh signaling in preadipocytes may account for the increased adipogenesis caused by BBS protein loss-of function.

The decision of preadipocytes to terminally differentiate may depend on ciliary signaling beyond Hh signaling. One pathway that may oppose antiadipogenic Hh signaling may be insulin-like growth factor 1 receptor (IGF1R) signaling. IGF1R, a receptor tyrosine kinase, is an important activator of both the expansion and differentiation of 3T3-L1 preadipocytes (Qiu et al. 2001; Xu and Liao 2004). IGF1R phosphorylates its adapter protein, insulin receptor substrate 1 (IRS1), to indirectly activate AKT1, a serine/threonine protein kinase involved in adipocyte metabolism (Fischer-Posovszky et al. 2012). Activated IGF1R localizes to 3T3-L1 cilia, and activated IRS1 and AKT1 to the basal body (Zhu et al. 2009),

suggesting an important role for cilia in sensitizing preadipocytes to the prodifferentiative effects of insulin. Consistent with this hypothesis, inhibiting ciliogenesis by knockdown of either *Ift88* or *Kif3a* inhibits the activation of IGF1R or AKT1 in 3T3-L1 preadipocytes the same (Zhu et al. 2009)

In addition to effects on the differentiation of preadipocyte into mature adipocytes, ciliary signaling may impact adipogenesis through regulation of cellular metabolism. Stimulating 3T3-L1 adipocytes with Sonic Hedgehog ligand promoted aerobic glycolysis on a time scale inconsistent with a transcriptional effect, suggesting that Hh signals can impact metabolism through Gli-independent “noncanonical” mechanisms (Teperino et al. 2012).

Could disruption of a nontranscriptional, noncanonical ciliary Hh signaling pathway decrease aerobic glycolysis and thereby at least partially account for how ciliary defects cause obesity? SAG and cyclopamine, two small molecules that promote ciliary localization of Smo but have opposite effects on the Gli-dependent Hh transcriptional program, both promote glucose uptake in 3T3-L1 cells (Teperino et al. 2012). Moreover, cyclopamine increases glucose uptake by mouse brown adipose tissue and muscle in vivo and increases core body temperature by ~1°C, consistent with increased thermogenesis. It will be interesting to determine whether genetic removal of Smo or cilia from brown adipose tissue and muscle blocks these effects, confirming that cyclopamine acts through a ciliary Hh pathway to activate thermogenesis.

One way that ciliary Smo may affect metabolism is through AMP-activated protein kinase (AMPK), a critical regulator of cellular energy homeostasis. Pharmacological stimulation of Smo activated AMPK in a way that was dependent on *Ift88* and *Kif3a*, two genes required for ciliogenesis (Teperino et al. 2012). AMPK and its upstream regulator, LKB1, have been identified as proteins that can, at least partially, localize to cilia (Boehlke et al. 2010; Mick et al. 2015), further suggesting that Smo may regulate AMPK at the cilium. However, small molecule antagonists of Smo that block its localization to cilia also induced AMPK activation, indicating that the cilium may not be crucial for Hh-mediated modulation of AMPK (Teperino et al. 2012). In contrast to Hh pathway stimulation, AMPK reduces glucose uptake and restricts aerobic glycolysis, at least in some cell types (Faubert et al. 2013), suggesting that the effects of Hh signaling on metabolism may be at least partly mediated through an AMPK-independent mechanism. Although neuronal cilia clearly have important roles in satiety control, alterations in ciliary signaling in preadipocytes, adipocytes, or muscle may contribute to ciliopathy-associated obesity, a possibility that remains to be examined in ciliopathy models.

CONCLUSIONS

Important questions about the pathogenesis of ciliopathy-associated obesity concern some of the following: which tissues are involved, which signaling pathways are involved, and whether the obesity arises from developmental or physiological changes. Conditional genetic ablation of the primary cilia in mice has established that neuronal primary cilia suppress feeding behavior, suggesting that some form of ciliary signaling promotes satiety. A clear hypothesis is that human ciliopathy mutations could alter the localization and/or function of

receptor(s) involved in energy homeostasis at the primary cilia. While LEPR is an excellent candidate for such a role, it may not be one of the direct culprits. Moreover, it is not yet clear whether the obesity caused by these mutations results from a developmental or postdevelopmental alteration of cilia function, with the possibility that it may be both. Of interest will be the systematic conditional removal of both ciliogenic and BBS-associated genes in adult hypothalamic neuronal populations implicated in feeding behavior to elucidate which neurons possess the cilia that function in appetite and satiety.

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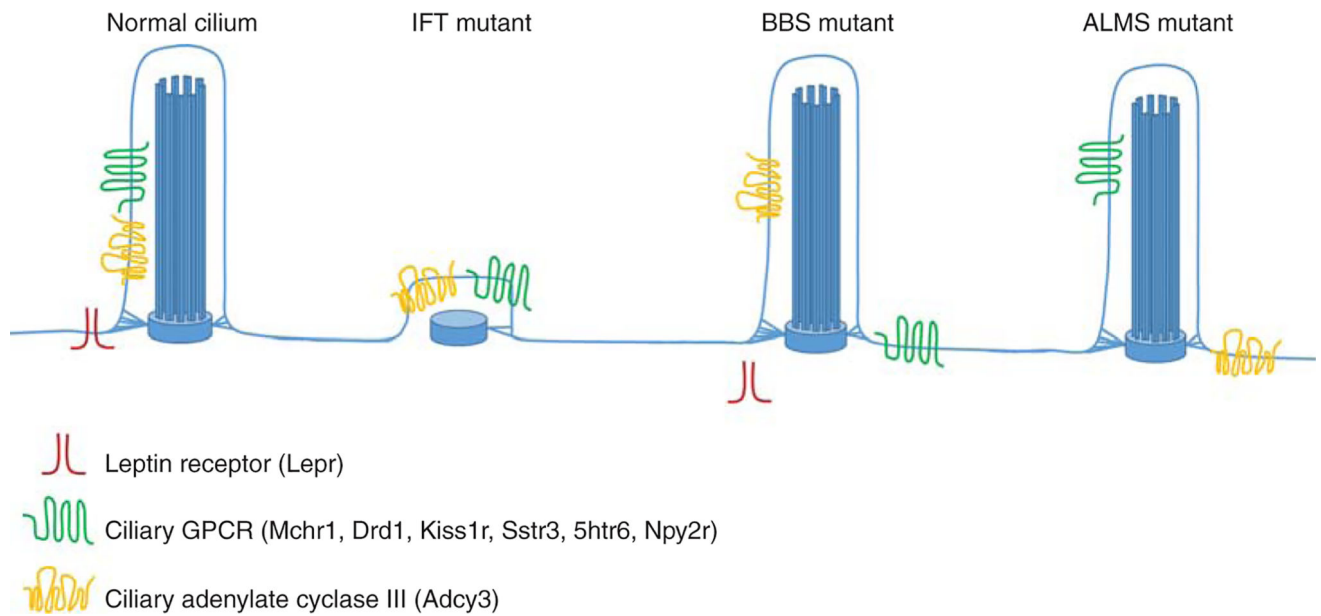


Figure 1.

Model of how ciliary signaling may contribute to energy homeostasis. Certain G-protein-coupled receptors (GPCRs) and signaling machinery, such as Sstr3, Mchr1, Drd1, Kiss1r, Htr6, and Adcy3, localize to the cilia membrane of neurons in specific brain regions. Intraflagellar transport (IFT) mutation results in loss of the cilium. In mouse models of Bardet – Biedl syndrome (BBS), both ciliary GPCRs and membrane-associated Lepr localization are perturbed. In Alström syndrome (ALMS) mouse models, GPCRs remain at cilia, but Adcy3 no longer localizes appropriately to cilia. Taken together, these models convey the complexity of the cilium as a signaling center and indicate that there are differing requirements for membrane protein localization to cilia.

Table 1

Cilia Associated Mouse Models of Obesity

Gene	Allele (MGI)	Type of Allele	Mouse Phenotypes	References
<i>Adcy3</i>	<i>Adcy3^{tm1Drs}</i>	Knock-out	Obesity, anosmia	Wang et al. 2009
<i>Adcy3</i>	<i>Adcy3^{fl}</i>	ENU gain-of-function	Resistant to diet-induced obesity, less adipose	Pitman et al. 2014
<i>Alms1</i>	<i>Alms1^{Gt(XH152)Byg}</i>	Genetrap	Obesity, retinopathy, male infertility, late onset hearing loss	Collin et al. 2005
<i>Alms1</i>	<i>Alms1^{f^{oz}}</i>	Spontaneous	Obesity, male infertility, late onset hearing loss	Arsov et al. 2006
<i>Bbs1</i>	<i>Bbs1^{tm1Vcs}</i>	Knock-in	Obesity, retinopathy, male infertility, ventriculomegaly	Davis et al. 2007
<i>Bbs2</i>	<i>Bbs2^{tm1Vcs}</i>	Knock-out	Obesity, retinopathy, renal cysts, male infertility, anosmia, social submissiveness, ventriculomegaly	Nishimura et al. 2004; Davis et al. 2007
[†] <i>Bbs3/Arl6</i>	<i>Arl6^{tm2Vcs}</i>	Knock-out	Increased fat mass, retinopathy, male infertility, hydrocephalus, elevated blood pressure	Zhang et al. 2011
[*] <i>Bbs4</i>	<i>Bbs4^{tm1Vcs}</i>	Knock-out	Obesity, retinopathy, male infertility, social submissiveness, ventriculomegaly	Mykytyn et al. 2004; Nishimura et al. 2004; Davis et al. 2007
[*] <i>Bbs4</i>	<i>Bbs4^{Gt1Nk}</i>	Genetrap	Obesity (sex dependent penetrance and severity), retinopathy, social submissiveness, increased anxiety	Eichers et al. 2006
<i>Bbs6/Mkks</i>	<i>Mkks^{tm1Vcs}</i>	Knock-out	Obesity, retinopathy, male infertility, anosmia, elevated blood pressure, social submissiveness, ventriculomegaly	Fath et al. 2005; Davis et al. 2007
<i>Bbs7</i>	<i>Bbs7^{tm1Vcs}</i>	Knock-out	Obesity, male infertility, ventriculomegaly	Zhang et al. 2013
<i>Bbs8/Ttc8</i>	<i>Ttc8^{tm1Reed}</i>	Knock-out	Obesity, anosmia, retinal degeneration, renal tubule anomalies	Tadenev et al. 2011
<i>Bbs11/Trim32</i>	<i>Trim32^{Gt(BGA355)Byg}</i>	Genetrap	Increased body weight, muscular myopathy	Kudryashova et al. 2009
<i>Bbs12</i>	<i>Bbs12^{tm1.1Vmar}</i>	Knock-out	Obesity, retinal degeneration	Marion et al. 2012
<i>Ift88</i>	<i>Ift88^{tm1.1Bky}</i>	Conditional Knock-out	Obesity, renal cysts, hepatic cysts	Davenport et al. 2007
<i>Kif3a</i>	<i>Kif3a^{tm1Gsn}</i>	Conditional Knock-out	Obesity, renal cysts, hepatic cysts	Davenport et al. 2007
<i>Rpgrip11</i>	<i>Rpgrip11^{tm1a(EUCOMM)Wtsi}</i>	Knock-out	Obesity	Stratigopoulos et al. 2014

[†] *Bbs3* mutant mice do not become obese, but do display increased fat mass. Likewise, *Bbs11* mutant mice have not been reported to be obese, but do display a significant and persistent increase in body weight starting at 2 months of age.

^{*} Two different *Bbs4*^{-/-} knockout mouse lines have been independently generated and different penetrance and severity of obesity have been reported for each.